

What is claimed is:

1. A method for manufacture of a medicament for use in treating a diabetic subject, the medicament comprising a composition for islet neogenesis therapy and an agent for suppressing an immune response.

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2. The method according to claim 1, wherein the composition for islet neogenesis therapy comprises an EGF receptor ligand.

3. A method according to claim 1, further comprising at least two agents for suppressing  
10 an immune response.

4. The method according to any of claims 1-3, wherein the composition for islet neogenesis therapy comprises a gastrin/cholecystekinin (CCK) receptor ligand.

15 5. The method according to claim 2, wherein the EGF receptor ligand is a recombinant human EGF.

6. The method according to claim 2, wherein the EGF receptor ligand is EGF51N.

20 7. The method according to claim 4, wherein the gastrin/CCK receptor ligand is human gastrin17.

8. The method according to claim 1, wherein the agent for suppressing immune response is a drug.

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9. The method according to claim 1, wherein the agent for suppressing immune response is at least one selected from of the group consisting of a rapamycin; a corticosteroid; an azathioprine; mycophenolate mofetil; a cyclosporine; a cyclophosphamide; a methotrexate; a 6-mercaptopurine; FK506 (Tacrolimus); 15-deoxyspergualin; an FTY 720; 30 a mitoxantrone; a 2-amino-1,3-propanediol; a 2-amino-2[2-(4-octylphenyl)ethyl]propane-

1,3-diol hydrochloride; a 6-(3-dimethyl-aminopropionyl) forskolin; and a demethimmunomycin.

10. The method according to claim 9, wherein the rapamycin is Everolimus or Sirolimus.

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11. The method according to claim 9, wherein the corticosteroid is dexamethasone.

12. The method according to claim 1, wherein the agent for suppressing immune response is a protein.

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13. The method according to claim 12, wherein the protein comprises an amino acid sequence of an antibody.

14. The method according to claim 1, wherein the agent for suppressing immune response is at least one selected from the group consisting of: hu1 124; BTI-322; allotrap-HLA-B270; OKT4A; Enlimomab; ABX-CBL; OKT3; ATGAM; basiliximab; daclizumab; antithymocyte immunoglobulin; ISAtx247; Medi-500; Medi-507; Alefacept; efalizumab; infliximab; and an interferon.

20 15. The method according to claim 1, wherein in manufacture of the medicament, the islet neogenesis therapy composition and the agent for suppressing immune response are formulated for sequential administration.

25 16. The method according to claim 15 wherein in manufacture of the medicament, the composition and the agent are formulated for storage during a period of time of at least one day between administering the agent and administering the composition.

30 17. The method according to claim 15 wherein in manufacture of the medicament, the composition and the agent are formulated for storage during a period of time of at least one week between administering the agent and administering the composition.

18. The method according to claim 15 wherein in manufacture of the medicament, the composition and the agent are formulated for storage during a period of time of at least six weeks between administering the agent and administering the composition.

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19. The method according to claim 1, wherein in manufacture of the medicament, at least one of the islet neogenesis therapy composition and the agent for suppressing immune response are formulated for systemic administration.

10 20. The method according to claim 19, wherein in manufacture of the medicament, at least one of the islet neogenesis therapy composition and the agent for suppressing immune response are formulated for bolus administration.

15 21. The method according to claim 1, wherein in manufacture of the medicament, at least one of the islet neogenesis therapy composition and the agent for suppressing immune response are formulated for administration by a route selected from the group consisting of intravenous, subcutaneous, intraperitoneal, and intramuscular.

20 22. The method according to claim 1, wherein in manufacture of the medicament, at least one of the islet neogenesis therapy composition and the agent for suppressing immune response are formulated for oral administration.

25 23. The method according to claim 1, wherein in manufacture of the medicament, the agent for suppressing immune response is formulated to contain at least one selected from the group of Sirolimus, Tacrolimus, Everolimus, ISAtx247, and daclizumab.

24. The method according to claim 1, wherein in manufacture of the medicament, the agent for suppressing immune response is formulated for administration to a diabetic mammal.

25. The method according to claim 1, wherein in manufacture of the medicament, the agent for suppressing immune response is formulated for administration to a human.

5 26. A method for manufacture of a medicament for use in treating a diabetic subject, the medicament comprising a composition for islet neogenesis therapy consisting of at least one of an EGF receptor ligand and a gastrin/CCK receptor ligand, and at least one immunosuppressing agent.

10 27. The method according to claim 26, wherein the medicament is formulated to comprise the gastrin/CCK receptor ligand and the at least one immunosuppressing agent in the absence of the EGF receptor ligand.

15 28. The method according to claim 27, wherein the medicament is formulated to administer the gastrin/CCK receptor ligand and the at least one immunosuppressing agent in the absence of the EGF receptor ligand, and the method further comprises a period of no administration of any of the agent or the composition.

20 29. The method according to claim 26, wherein the medicament is formulated for a diabetic subject having recent onset diabetes.

30. The method according to claim 28, wherein the medicament is formulated for sequential administration of the composition and the agent.

25 31. The method of claim 26, wherein the medicament is formulated so that each of the EGF receptor ligand, the gastrin/CCK receptor ligand, and the immunosuppressing agent are in an effective dose.

30 32. The method of any of claims 1 and 26, wherein the composition or agent is further formulated to comprise a pharmaceutically acceptable buffer.

33. A method for manufacture of a medicament for use in treating a diabetic subject, the medicament comprising a composition for islet neogenesis therapy consisting of at least one of EGF51N and gastrin17, and at least one immunosuppressing agent.

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34. A method according to claim 33, wherein the medicament is formulated so that the agent is an effective dose of each of Tacrolimus and Sirolimus.

10 35. A method according to claim 33, wherein the medicament is formulated to comprise an effective dose of at least one of EGF51N and gastrin17, and an effective dose of at least one of Tacrolimus, Everolimus, daclizumab, ISAtx247, and Sirolimus.

15 36. A method for manufacture of a medicament for use in treating a diabetic subject, the medicament comprising a gastrin/CCK receptor ligand and an agent for suppressing an immune response.

37. The method according to claim 36, wherein the gastrin/CCK receptor ligand is gastrin17.

20 38. The method according to claim 36, wherein the agent for suppressing immune response is a drug.

25 39. The method according to claim 36, wherein the agent for suppressing immune response is selected from at least one of the group consisting of a rapamycin; a corticosteroid; an azathioprine; mycophenolate mofetil; a cyclosporine; a cyclophosphamide; a methotrexate; a 6-mercaptopurine; an FK506; an ISAtx247; a 15-deoxyspergualin; an FTY 720; a mitoxantrone; a 2-amino-1,3-propanediol; a 2-amino-2[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride; a 6-(3-dimethyl-aminopropionyl)forskolin; and a demethimmunomycin.

40. The method according to claim 39, wherein the rapamycin is Sirolimus or Everolimus.

41. The method according to claim 39, wherein the corticosteroid is dexamethasone.

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42. The method according to claim 36, wherein the agent for suppressing immune response is a protein.

43. The method according to claim 42, wherein the protein comprises an amino acid sequence of an antibody.

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44. The method according to claim 43, wherein the agent for suppressing immune response is at least one selected from the group consisting of: hu124; BTI-322; allotrap-HLA-B270; OKT4A; Enlimomab; ABX-CBL; OKT3; ATGAM; basiliximab; daclizumab; 15 antithymocyte immunoglobulin; ISAtx247; Medi-500; Medi-507; Alefacept; efalizumab; and infliximab.

45. The method according to claim 36, wherein the gastrin/CCK receptor ligand and the agent for suppressing immune response are administered sequentially.

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46. The method according to claim 36, wherein the gastrin/CCK receptor ligand is formulated for bolus administration.

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47. The method according to claim 36, wherein the receptor ligand is formulated for administration by a route selected from the group consisting of intravenous, subcutaneous, intraperitoneal, and intramuscular.

48. The method according to claim 36, wherein the agent for suppressing immune response is formulated for administration by a route selected from the group consisting of an

oral, systemic, intravenous, subcutaneous, intraperitoneal, and intramuscular routes of delivery.

49. The method according to claim 36, wherein the agent for suppressing immune response is selected from at least one of Tacrolimus, ISAtx247, Everolimus, Sirolimus, and daclizumab.

50. The method according to any of claims 1, 26, 33, and 36, further comprising measuring a physiological parameter in the subject selected from the group of measuring level of: fasting blood glucose; pancreatic insulin content; pancreatic  $\beta$  cell content; and plasma insulin C peptide.

51. The method according to claim 36, wherein the medicament is formulated for a subject that is a mammal.

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52. The method according to claim 36, wherein the medicament is formulated for a subject that is a diabetic mammal.

53. The method according to claim 36, wherein the medicament is formulated for a subject that is a diabetic mammal with recent onset diabetes.

54. The method according to claim 36, wherein the medicament is formulated for a subject that is a human.

25 55. A method for manufacture of a medicament for use in treating a diabetic subject, the medicament having a composition comprising an effective dose of gastrin17 and an effective dose of at least one immunosuppressing agent.

56. A method according to claim 55, wherein the at least one immunosuppressing agent is  
30 Tacrolimus or Sirolimus.

57. A method according to claim 56, the medicament further comprising an effective dose of ISAtx247 or daclizumab.

5 58. The method according to any according to any of claims 55-57, wherein the medicament further includes a pharmaceutically acceptable buffer.

59. A pharmaceutical composition comprising an agent for suppressing an immune response and at least one of an EGF receptor ligand and a gastrin/CCK receptor ligand.

10 60. The composition according to claim 59, wherein the gastrin/CCK receptor ligand is a gastrin.

15 61. The composition according to claim 59, wherein the gastrin/CCK receptor ligand is a gastrin17.

62. The composition according to claim 61, wherein the gastrin17 is gastrin17Met15 or gastrin17Leu15.

20 63. The composition according to claim 59, wherein the EGF receptor ligand is EGF.

64. The composition according to claim 59, wherein the EGF is recombinant human EGF51N.

25 65. The composition according to claim 59, wherein the agent for suppressing immune response is a drug.

66. The composition according to claim 59, wherein the agent for suppressing immune response is at least one selected from of the group consisting of a rapamycin; a

corticosteroid; an azathioprine; mycophenolate mofetil; a cyclosporine; a cyclophosphamide; a methotrexate; a 6-mercaptopurine; FK506 (Tacrolimus); 15-deoxyspergualin; an FTY 720; a mitoxantrone; a 2-amino-1,3-propanediol; a 2-amino-2[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride; a 6-(3-dimethyl-aminopropionyl) forskolin; and a  
5 demethimmunomycin.

67. The composition according to claim 59, wherein the agent for suppressing immune response is a protein.

10 68. The composition according to claim 59, wherein the agent for suppressing immune response is a portion of an antibody.

69. The composition according to claim 59, wherein the agent for suppressing immune response is at least one selected from the group consisting of: hu124; BTI-322; allotrap-  
15 HLA-B270; OKT4A; Enlimomab; ABX-CBL; OKT3; ATGAM; basiliximab; daclizumab; antithymocyte immunoglobulin; ISATx247; Medi-500; Medi-507; Alefacept; efalizumab; infliximab; and an interferon.

70. A kit for treatment of a diabetic subject, comprising a composition for islet  
20 neogenesis therapy, an immunosuppressive agent, and a container.

71. A kit comprising at least one dose of a composition according to any of claims 59-69.

72. A kit according to any of claims 70-72, further comprising instructions for use.

25 73. A method of manufacture of a medicament for use in treating a diabetic subject, the method comprising manufacture of a composition comprising an effective dose of gastrin17 and an effective dose of at least one immunosuppressing agent.

74. A method of manufacture of a medicament for use in treating a diabetic subject, the method comprising manufacture of a medicament comprising an effective dose of gastrin17 and an effective dose of each of Tacrolimus and Sirolimus.

5 75. Use of an effective dose of each of gastrin17 and at least one immunosuppressing agent in manufacture of a composition for treating a diabetic subject.

76. Use of an effective dose of gastrin17 and an effective dose of each of Tacrolimus and Sirolimus in manufacture of a medicament for treating a diabetic subject.

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77. Use of an immunosuppressing agent and at least one of an EGF receptor ligand and a gastrin/CCK receptor ligand for the manufacture of a medicament for treating a diabetic subject.

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